Original Study

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Real-world Effectiveness and Safety of Pazopanib in Patients With Intermediate Prognostic Risk Advanced Renal Cell Carcinoma

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Abstract

Patients with intermediate-risk advanced renal cell carcinoma are a heterogeneous population, having either 1 or 2 risk factors. It is unclear whether all patients in this risk category should be treated similarly. A secondary analysis of the PRINCIPAL study of pazopanib found that patients can be stratified by number of risk factors and Eastern Cooperative Oncology Group performance status to more accurately predict outcomes.

Introduction: The objective of this study was to determine the effectiveness and safety of pazopanib in patients with intermediate-risk advanced/metastatic renal cell carcinoma in the PRINCIPAL study (NCT01649778). **Patients and Methods:** Patients had clear-cell advanced/metastatic renal cell carcinoma and met intermediate-risk International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) and Memorial Sloan Kettering Cancer Center (MSKCC) criteria. Assessments included progression-free survival, overall survival, objective response rate, and safety. We also evaluated effectiveness based on number of risk factors, age, and performance status (PS), as well as safety in older and younger patients. **Results:** Three hundred sixty three and 343 intermediate-risk MSKCC and IMDC patients were included, respectively. The median progression-free survival was 13.8 months (95% confidence interval [CI], 10.7-18.1 months) and 7.4 months (95% CI, 6.2-10.3 months) for patients with 1 and 2 MSKCC risk factors, respectively, and 13.1 months (95% CI, 10.7-18.1 months) and 8.1 months (95% CI, 6.4-10.7 months) for patients with 1 and 2 IMDC risk factors, respectively. The median overall survival was not reached and was 15.2 months (95% CI, 12.3-26.5 months) for patients with 1 and 2 MSKCC risk factors, respectively, and 33.9 months (95% CI, 33.9 months to not estimable) and 19.4 months (95% CI, 14.3 months to not estimable) with 1 and 2 IMDC risk factors, respectively. A lower overall response rate was observed with Eastern Cooperative Oncology Group PS $\geq$ 2 (vs. PS $<$ 2). All-grade treatment-related adverse events occurred in approximately 63% of patients, and the safety profile among older and younger patients was similar. **Conclusions:** Outcomes with pazopanib in intermediate-risk patients suggest that patients can be further stratified by number of risk factors (1 vs. 2) and Eastern Cooperative Oncology Group PS ($<$ 2 vs. $\geq$ 2) to more accurately predict outcomes.

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Introduction

Clinical outcomes for patients with advanced renal cell carcinoma (RCC) have improved markedly since the introduction of agents targeting vascular endothelial growth factor and its receptor, mammalian target of rapamycin inhibitors, and immuno-oncologic agents.[1] Cytokine treatment was the standard of care prior to the introduction of molecular targeted agents, and during that era, a prognostic model was developed to predict survival in patients treated with interferon-α in clinical trials at the Memorial Sloan Kettering Cancer Center (MSKCC).[2] The MSKCC model utilizes 5 clinical and laboratory pretreatment factors that independently predict overall survival (OS) to categorize patients into favorable-risk (0 risk factors), intermediate-risk (1-2 risk factors), or poor-risk (≥ 3 risk factors) prognostic groups.[2] Although developed during the cytokine era, the MSKCC prognostic model has since been validated for use with targeted agents.[3] The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model is another prognostic model developed from patients treated with first-line vascular endothelial growth factor-targeted therapy (N = 645) and comprises 6 pretreatment clinical and laboratory factors.[4] Similar to the MSKCC model, the IMDC model groups patients into favorable-risk (0 risk factors), intermediate-risk (1-2 risk factors), or poor-risk (≥ 3 risk factors) groups, with significant differences in survival across risk groups.[4] The MSKCC and IMDC risk classifications are widely used to estimate prognosis and are becoming increasingly important for selecting treatments for patients with advanced RCC, as evidenced by several new agents now available for patients with intermediate- or poor-risk RCC.[5,6]

Even as the tyrosine kinase inhibitors pazopanib and sunitinib are standard first-line treatment options for patients with advanced RCC,[7,8] the phase III CheckMate-214 study recently demonstrated superiority of nivolumab plus ipilimumab over sunitinib in patients with IMDC intermediate or poor risk.[5] Conversely, patients with favorable risk in CheckMate-214 had significantly better outcomes (progression-free survival [PFS] and objective response rate [ORR]) with sunitinib compared with nivolumab plus ipilimumab in an exploratory analysis.[5] Approximately one-half of patients with advanced RCC have MSKCC or IMDC intermediate risk,[4,9-11] and discordant results between the favorable- and intermediate-risk populations in CheckMate-214[5] suggest that intermediate-risk patients may be further stratified to more accurately predict treatment outcomes. Indeed, previous retrospective analyses in intermediate-risk patients have demonstrated survival differences between patients with 1 versus 2 risk factors,[10-12] supporting the heterogeneity of this patient subgroup and justifying further analyses in prospective datasets.

The large, prospective, observational PRINCIPAL study (NCT01649778) confirmed the efficacy and safety of pazopanib in a real-world clinical setting in 657 patients with advanced RCC.[13] The objective of this secondary analysis of PRINCIPAL was to evaluate the real-world effectiveness and safety of pazopanib within MSKCC and IMDC intermediate-risk group patients with advanced RCC.

Patients and Methods

Study Design and Patients

PRINCIPAL was a global, prospective, observational study of patients with advanced/metastatic RCC treated with frontline pazopanib. The study was designed to enroll ~500 to 700 patients over approximately 30 months. This sample size was chosen based on the expected precision for the outcomes of interest (< 5% for PFS, OS, and ORR) and the feasibility of enrolling the desired patient population over the enrollment period. Consecutive patients meeting eligibility criteria were enrolled at participating sites and followed for 30 months or until premature discontinuation owing to death, withdrawal of consent, loss to follow-up, or termination from study. Patients who permanently discontinued study treatment were followed for up to 30 months post-enrollment. Patients were considered to have completed the study if 30 months of follow-up were conducted, or if the patient died during the study treatment or follow-up period.

Patients aged ≥ 18 years who have advanced/metastatic RCC of clear-cell or predominantly clear-cell histology and who made a clinical decision to initiate pazopanib within 30 days of enrollment were eligible for participation in the PRINCIPAL study. These secondary analyses included only patients who met MSKCC or IMDC intermediate-risk criteria. Patients were classified as MSKCC intermediate risk if they had 1 or 2 of the following risk factors[2]: time from initial diagnosis to initiation of therapy < 1 year; Karnofsky performance status (KPS) < 80%; serum hemoglobin level < lower limit of normal (LLN); serum corrected calcium level > 10 mg/dL; and lactate dehydrogenase level > 1.5× upper limit of

Table 1 Intermediate-risk Patient Disposition

	MSKCC Intermediate Risk n = 363 (%)	IMDC Intermediate Risk n = 343 (%)
Patients who completed study	281 (77.4)	258 (75.2)
Completed 30 months follow-up	133 (36.6)	130 (37.9)
Deaths	148 (40.8)	128 (37.3)
Patients who discontinued study	82 (22.6)	85 (24.8)
Withdrawal of patient consent	31 (8.5)	32 (9.3)
Physician request	8 (2.2)	11 (3.2)
Lost to follow-up	29 (8.0)	27 (7.9)
Other	14 (3.9)	15 (4.4)

Abbreviations: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC = Memorial Sloan Kettering Cancer Center.

Table 2 Intermediate-risk Patient Baseline Demographics and Disease Characteristics

	MSKCC Intermediate Risk n = 363 (%)	IMDC Intermediate Risk n = 343 (%)
Median age, y (range)	67.0 (22.0-89.0)	67.0 (22.0-90.0)
Male	256 (70.5)	243 (70.8)
Race[a]		
White/Caucasian/European	347 (95.6)	323 (94.2)
Other	19 (5.2)	19 (5.5)
Unknown/declined to provide	0	2 (0.6)
Number of risk factors[b]		
1	147 (40.5)	171 (49.9)
2	141 (38.8)	133 (38.8)
Missing	75 (20.7)	39 (11.4)
ECOG performance status		
< 2	333 (91.7)	316 (92.1)
≥ 2	8 (2.2)	8 (2.3)
Not recorded	22 (6.1)	19 (5.5)
Median disease duration of RCC from initial diagnosis, y (range)	1.8 (0.0-27.9)	1.8 (0.0-27.9)
Median disease duration of locally advanced/metastatic RCC, y (range)	0.1 (0.0-23.1)	0.1 (0.0-23.1)
Metastases present	349 (96.1)	329 (95.9)
Median number of metastatic sites (range)	2.0 (0.0-15.0)	2.0 (0.0-15.0)
Location of metastatic sites		
Lung	241 (66.4)	225 (65.6)
Lymph nodes	117 (32.2)	112 (32.7)
Bone	93 (25.6)	88 (25.7)
Liver	53 (14.6)	45 (13.1)
Adrenal glands	43 (11.8)	39 (11.4)
Brain	16 (4.4)	14 (4.1)
Other	91 (25.1)	88 (25.7)
Prior nephrectomy	287 (79.1)	273 (79.6)
First-line systemic therapy	18 (5.0)	14 (4.1)
Interleukin-2	3 (0.8)	1 (0.3)
Interferon-α	8 (2.2)	6 (1.7)
Other	7 (1.9)	7 (2.0)
Adjuvant/neoadjuvant systemic therapy		
Adjuvant	2 (0.6)	3 (0.9)
Neoadjuvant	2 (0.6)	2 (0.6)
No	328 (90.4)	313 (91.3)
Not applicable	31 (8.5)	25 (7.3)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC = Memorial Sloan Kettering Cancer Center; RCC = renal cell carcinoma.
[a]Patients may have indicated more than one race category.
[b]Patients with one missing risk factor were excluded.

normal (ULN). Patients were classified as IMDC intermediate risk if they had 1 or 2 of the following risk factors[4]: time from initial diagnosis to initiation of therapy < 1 year; KPS < 80%; serum hemoglobin level < LLN; serum corrected calcium level > ULN; absolute neutrophil count > ULN; and platelet count > ULN. Missing KPS risk factor was imputed based on baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) score: if baseline ECOG PS < 2, then KPS risk factor = no; if baseline ECOG PS ≥ 2, then KPS risk factor = yes.

All patients provided informed consent, and the study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice, patient privacy requirements, and ethical principles outlined in the Declaration of Helsinki 2008.

Assessments

There were no visits or procedures mandated by the protocol. At the baseline visit, patient demographics, disease characteristics, and medical history were collected. Follow-up information was obtained

Table 3 Subgroup Analysis of PFS and OS in Patients With Intermediate Risk at Baseline[a]

	MSKCC Intermediate Risk		IMDC Intermediate Risk	
	Disease Progression or Death, N	Median (95% CI), mos	Disease Progression or Death, N	Median (95% CI), mos
Progression-free survival				
Number of risk factors[b]				
1	85/147	13.8 (10.7-18.1)	88/171	13.1 (10.7-18.1)
2	85/141	7.4 (6.2-10.3)	88/133	8.1 (6.4-10.7)
Age, y				
< 65	79/142	12.3 (9.0-16.4)	73/136	13.1 (10.3-18.4)
≥ 65	131/219	10.7 (9.0-13.8)	123/205	10.7 (9.0-13.1)
ECOG performance status				
< 2	189/333	11.2 (9.5-14.1)	177/316	11.8 (9.9-15.4)
≥ 2	8/8	5.6 (1.3-12.8)	8/8	2.3 (1.2-10.7)
Overall survival				
Number of risk factors[b]				
1	46/147	NR (NE-NE)	51/171	33.9 (33.9-NE)
2	77/141	15.2 (12.3-26.5)	66/133	19.4 (14.3-NE)
Age, y				
< 65	52/142	33.9 (27.0-33.9)	43/136	33.9 (NE-NE)
≥ 65	95/219	30.5 (19.9-NE)	84/205	32.9 (26.0-NE)
ECOG performance status				
< 2	132/333	33.9 (27.9-NE)	113/316	33.9 (30.5-NE)
≥ 2	6/8	9.5 (1.3-NE)	7/8	5.0 (1.2-12.8)

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC = Memorial Sloan Kettering Cancer Center; NE = not evaluable; NR = not reached.
[a]Analysis conducted in all treated (AT) population.
[b]Patients with 1 missing risk factor excluded.

approximately every 3 months (± 4 weeks). Participating physicians assessed tumor responses according to local processes and their own clinical judgement. Primary effectiveness measures were PFS, OS, and ORR (defined as complete response or partial response). Patients who received ≥ 1 dose of pazopanib were evaluable for PFS, OS, and safety analyses (all treated [AT] population). The measurable disease (MD) population comprised patients with measurable disease at baseline and was used for the ORR analysis.

Table 4 Subgroup Analysis of ORR in Patients With Intermediate Risk at Baseline[a]

	MSKCC Intermediate Risk			IMDC Intermediate Risk		
	ORR, n/N (%)	Median DOR, mos (95% CI)	Median TTR, mos (95% CI)	ORR, n/N (%)	Median DOR, mos (95% CI)	Median TTR, mos (95% CI)
Number of risk factors[b]						
1	42/124 (33.9)	15 (10.8-22.5)	3 (2.9-3.5)	44/143 (30.8)	14 (7.5-22.5)	3 (2.9-3.2)
2	44/129 (34.1)	7 (4.6-21.3)	3 (2.7-3.2)	39/119 (32.8)	7 (4.4-20.1)	3 (2.7-3.2)
Age, y						
< 65	40/123 (32.5)	14 (5.8-19.3)	3 (2.7-3.4)	43/117 (36.8)	15 (5.8-19.3)	3 (2.9-3.5)
≥ 65	62/190 (32.6)	14 (8.8-22.3)	3 (2.8-3.1)	53/178 (29.8)	11 (7.1-20.1)	3 (2.8-3.1)
ECOG performance status						
< 2	97/288 (33.7)	14 (7.2-19.1)	3 (2.9-3.1)	93/272 (34.2)	13 (7.2-17.1)	3 (2.9-3.1)
≥ 2	0/7 (0.0)	NA	NA	0/7 (0.0)	NA	NA

Abbreviations: DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; MSKCC = Memorial Sloan Kettering Cancer Center; NA = not applicable; ORR = objective response rate; TTR = time to response.
[a]Analysis conducted in measurable disease (MD) population.
[b]Patients with 1 missing risk factor excluded.

Table 5 Safety Summary

	MSKCC Intermediate Risk n = 363 (%)		IMDC Intermediate Risk n = 343 (%)	
	All-grade	Grade ≥ 3	All-grade	Grade ≥ 3
Any AE	276 (76.0)	158 (43.5)	263 (76.7)	154 (44.9)
Treatment-related	227 (62.5)	109 (30.0)	218 (63.6)	110 (32.1)
AESIs[a]	231 (63.6)	98 (27.0)	224 (65.3)	99 (28.9)
Treatment-related	210 (57.9)	86 (23.7)	203 (59.2)	89 (25.9)
SAEs	97 (26.7)	76 (20.9)	92 (26.8)	70 (20.4)
Treatment-related	38 (10.5)	31 (8.5)	34 (9.9)	28 (8.2)
Fatal SAEs	17 (4.7)	17 (4.7)	13 (3.8)	13 (3.8)
Treatment-related	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
AEs leading to treatment discontinuation	53 (14.6)	29 (8.0)	54 (15.7)	29 (8.5)
Treatment-related	39 (10.7)	21 (5.8)	43 (12.5)	24 (7.0)
AEs leading to dose adjustment/interruption	190 (52.3)	104 (28.7)	186 (54.2)	101 (29.4)

Abbreviations: AEs = adverse events; AESI = adverse events of special interest; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC = Memorial Sloan Kettering Cancer Center; SAEs = serious adverse events.
[a]AESIs were defined as any reports of new onset/worsened hypertension, cardiac dysfunction, thyroid dysfunction, evidence of liver toxicity, or any other AE resulting in a pazopanib dose modification or discontinuation.

Statistical Analyses

Continuous variables were reported as medians and ranges; categorical variables were reported as number and percentage of the total population. Evaluations were based on point estimates and 95% confidence intervals (CIs), and efficacy and safety analyses were stratified by baseline patient characteristics (eg, ECOG PS, histologic subtype). Formal hypothesis or statistical significance testing was not planned.

Results

Patients

Of the 657 enrolled patients in the PRINCIPAL study who received ≥ 1 dose of pazopanib (AT population), more than one-half had intermediate-risk criteria per MSKCC (55.3%; n = 363) and IMDC (52.2%; n = 343); MSKCC and IMDC risk data were missing for 178 (27.1%) and 128 (19.5%) patients in the overall population, respectively. Among the MSKCC and IMDC intermediate-risk patients, 281 (77.4%) and 258 (75.2%) completed the study, and 133 (36.6%) and 130 (37.9%) completed the 30-month follow-up. One hundred and forty-eight (40.8%) in the MSKCC intermediate-risk group and 128 (37.3%) in the IMDC intermediate-risk group died. Discontinuation rates were similar for both intermediate-risk groups (Table 1). Baseline patient demographics and disease characteristics for intermediate-risk patients are shown in Table 2. Per MSKCC and IMDC criteria, 1 risk factor was present for 147 (40.5%) and 171 (49.9%) patients, respectively, and 2 risk factors were present for 141 (38.8%) and 133 (38.8%) patients, respectively. Most patients had an ECOG PS of < 2.

Effectiveness

In both MSKCC and IMDC intermediate-risk groups, median PFS and OS were numerically longer for patients who had 1 risk factor compared with patients who had 2 risk factors. Median PFS was 13.8 months (95% CI, 10.7-18.1 months) and 7.4 months (95% CI, 6.2-10.3 months) for patients with 1 and 2 MSKCC risk factors, respectively, and 13.1 months (95% CI, 10.7-18.1 months) and 8.1 months (95% CI, 6.4-10.7 months) for patients with 1 and 2 IMDC risk factors, respectively (Table 3). Within these intermediate-risk populations, the median OS was not reached and was 15.2 months (95% CI, 12.3-26.5 months) for patients with 1 and 2 MSKCC risk factors, respectively, and 33.9 months (95% CI, 33.9 months to not estimable) and 19.4 months (95% CI, 14.3 months to not estimable) for patients with 1 and 2 IMDC risk factors, respectively (Table 3). Shorter median PFS and OS were observed in patients with ECOG PS ≥ 2 (vs. PS < 2) (Table 3).

Among patients with intermediate-risk, a lower ORR was observed for those with ECOG PS ≥ 2 (vs. PS < 2). For patients with ECOG PS < 2, the ORR was 33.7% and 34.2% by MSKCC and IMDC intermediate-risk criteria, respectively, compared with 0% for patients with ECOG PS ≥ 2 by both MSKCC and IMDC intermediate-risk criteria (Table 4).

Table 6 Treatment-related Adverse Events

Any Grade Occurring in ≥ 5% of Patients in Either Group	MSKCC Intermediate Risk n = 363 (%)	IMDC Intermediate Risk n = 343 (%)
Hypertension	86 (23.7)	82 (23.9)
Diarrhea	45 (12.4)	47 (13.7)
ALT increased	45 (12.4)	42 (12.2)
AST increased	28 (7.7)	26 (7.6)
Hypothyroidism	21 (5.8)	24 (7.0)
Nausea	19 (5.2)	16 (4.7)
Blood TSH increased	15 (4.1)	18 (5.2)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; TSH = thyroid-stimulating hormone.

Table 7 Adverse Events by Age (< 65 Versus ≥ 65 Years)

Any Grade Occurring in ≥ 5% of Patients in any Group	MSKCC Intermediate Risk n = 363 (%)		IMDC Intermediate Risk n = 343 (%)	
	< 65 Years n = 143	≥ 65 Years n = 220	< 65 Years n = 137	≥ 65 Years n = 206
Hypertension	38 (26.6)	52 (23.6)	41 (29.9)	47 (22.8)
ALT increased	21 (14.7)	25 (11.4)	19 (13.9)	24 (11.7)
Diarrhea	18 (12.6)	30 (13.6)	23 (16.8)	27 (13.1)
AST increased	15 (10.5)	15 (6.8)	14 (10.2)	13 (6.3)
Blood TSH increased	13 (9.1)	9 (4.1)	16 (11.7)	9 (4.4)
Nausea	11 (7.7)	11 (5.0)	10 (7.3)	9 (4.4)
Vomiting	9 (6.3)	6 (2.7)	7 (5.1)	4 (1.9)
Hypothyroidism	8 (5.6)	14 (6.4)	9 (6.6)	17 (8.3)
Asthenia	5 (3.5)	11 (5.0)	5 (3.6)	9 (4.4)
Fatigue	3 (2.1)	11 (5.0)	2 (1.5)	10 (4.9)
Hepatotoxicity	2 (1.4)	12 (5.5)	3 (2.2)	13 (6.3)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; TSH = thyroid-stimulating hormone.

Safety

At least 1 adverse event (AE) was reported by most patients with intermediate risk (MSKCC, 76.0%; IMDC, 76.7%), and most AEs were related to treatment (MSKCC, 62.5%; IMDC, 63.6%) (Table 5). The most commonly reported treatment-related AEs (≥ 5%) in the MSKCC and IMDC intermediate-risk groups were hypertension, diarrhea, increased alanine aminotransferase, increased aspartate aminotransferase, hypothyroidism, nausea, and increased blood thyroid-stimulating hormone (Table 6). Treatment-related serious AEs were reported by 38 (10.5%) MSKCC intermediate-risk patients and 34 (9.9%) IMDC intermediate-risk patients. Seventeen (4.7%) and 13 (3.8%) patients died in the MSKCC and IMDC intermediate-risk groups, respectively; 1 (0.3%) death in each intermediate-risk group was considered related to treatment. When pazopanib safety was assessed in intermediate-risk patients aged ≥ 65 and < 65 years, the AE profile was generally similar between the 2 age groups (Table 7).

Discussion

Prognostic risk models based on clinical and laboratory factors not only predict survival for patients with advanced RCC but also have become important tools to guide treatment choice in a crowded therapeutic landscape. New treatment options have recently emerged for intermediate- or poor-risk patients[5,6]; however, it is unclear whether all intermediate-risk patients, who comprise a heterogeneous patient group with 1 or 2 risk factors, should be treated similarly. Such differential efficacy outcomes between risk groups have been previously demonstrated in the CheckMate-214 trial, for example.[5] In CheckMate-214, nivolumab plus ipilimumab showed superior OS and ORR versus sunitinib in intermediate-/poor-risk patients (co-primary endpoints). Conversely, PFS and ORR favored sunitinib in an exploratory analysis of favorable-risk patients[5]; however, the difference in ORR between treatment groups was no longer significant in an updated analysis after a minimum of 30 months' follow-up (updated PFS not reported).[14]

The current secondary analysis of the PRINCIPAL study investigates intermediate-risk subgroups for differences in outcomes. An earlier primary analysis of the PRINCIPAL study demonstrated that the PFS of the overall MSKCC and IMDC intermediate-risk patients was 11.2 months (95% CI, 9.5-13.7 months) and 11.6 months (95% CI, 9.8-14.1 months), respectively; OS was 33.9 months (95% CI, 26.9 months to not reached) and 32.9 months (95% CI, 28.6 months to not reached), respectively. In this large prospective real-world study, intermediate-risk patients with 1 risk factor by both MSKCC and IMDC criteria had longer median PFS and OS with pazopanib compared with patients with 2 risk factors. Clinical outcomes were also worse for patients with poor ECOG PS (≥ 2) versus patients with ECOG PS < 2. These results highlight the heterogeneity of the intermediate-risk group. Further, our findings are consistent with previous retrospective analyses of intermediate-risk advanced RCC patients undergoing targeted therapy, which found prolonged PFS and OS in patients with 1 risk factor compared with 2 risk factors[10-12] and in patients with poorer ECOG PS (0 vs. 1-2).[11] Findings from the secondary analysis of the PRINCIPAL study suggest that patients with advanced RCC of intermediate prognostic risk can be further stratified, by 1 risk factor (intermediate-low) versus 2 risk factors (intermediate-high) or ECOG PS to more accurately predict treatment outcomes. These findings may further aid treatment choice for patients classified as having intermediate risk, particularly if applied to clinical trials of immuno-oncologic regimens versus tyrosine kinase inhibitor therapy.

Pazopanib treatment among intermediate-risk patients was generally well-tolerated. A relatively low frequency of hypertension, diarrhea, alanine aminotransferase elevations, and aspartate aminotransferase elevations were observed compared with past clinical trial data, possibly owing to the observational nature of PRINCIPAL. Further, we noted similar safety profiles for patients in the older (≥ 65 years) and younger (< 65 years) age groups, which supports a role for pazopanib in the treatment of patients of all ages with advanced RCC.

Conclusions

Patients with intermediate-risk advanced RCC treated with pazopanib in the prospective observational PRINCIPAL study

could be further stratified by number of risk factors (1 vs. 2) and ECOG PS (< 2 vs. ≥ 2) to more accurately predict effectiveness outcomes. It should be noted that only a small group of patients with ECOG PS ≥ 2 were included in our analyses. The results have implications for treatment choice in intermediate-risk patients, who are currently prescribed similar treatments regardless of the number or type of risk factors or PS.

Clinical Practice Points

- Prognostic risk models such as those developed by MSKCC and the IMDC are important tools for guiding treatment choices for patients with advanced RCC.
- With the emergence of newer treatments for patients with intermediate- or poor-risk RCC, it has become unclear whether all intermediate-risk patients should be treated similarly, given that this population comprises a heterogenous group having either 1 or 2 risk factors.
- A secondary analysis of the prospective PRINCIPAL study was conducted to evaluate real-world effectiveness and safety of pazopanib within MSKCC and IMDC intermediate-risk group patients according to subgroups by number of risk factors (1 vs. 2), age (< 65 vs. ≥ 65 years) and ECOG PS (< 2 vs. ≥ 2).
- Patients with MSKCC or IMDC intermediate risk having 1 risk factor had longer median PFS and OS with pazopanib than patients with 2 risk factors. Similar clinical outcomes were seen in patients with ECOG PS < 2 in comparison to those with ECOG PS ≥ 2.
- Results of this secondary analysis highlight the heterogeneity of the intermediate-risk group and suggest that these patients can be further stratified, either by number of risk factors (1 = intermediate-low vs. 2 = intermediate-high) or ECOG PS, to more accurately predict treatment outcomes.
- These findings provide important considerations concerning treatment choices for patients classified as having intermediate-risk RCC, and further have potential implications for future clinical trials of immuno-oncologic regimens versus TKI therapies.

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Disclosure

G. Procopio reports a consulting or advisory role for Bristol-Myers Squibb, Ipsen, Novartis, and Pfizer; speakers' bureau for Bayer, Bristol-Myers Squibb, Ipsen, and Novartis; and research funding from Ipsen and Novartis. A. Bamias reports honoraria from Bristol-Myers Squibb, Novartis, Pfizer, and Roche; consulting or advisory role with Bristol-Myers Squibb, Novartis, Pfizer, and Roche; research funding from Bristol-Myers Squibb, Novartis, and Roche; and travel, accommodations, and expenses from Novartis. M. Schmidinger reports honoraria from Bristol-Myers Squibb, Eisai, Exelixis, Ipsen, Novartis, Pfizer, Roche, and EUSA; consulting or advisory role for Bristol-Myers Squibb, Eisai, Exelixis, Ipsen, Novartis, Pfizer, Roche, and EUSA; research funding from Roche; and travel, accommodation, and expenses from Pfizer and Roche. R. Hawkins reports employment with Cellular Therapeutics and Immetacyte Limited; leadership with Cellular Therapeutics and Immetacyte Limited; stock or other ownership in Cellular Therapeutics and Immetacyte Limited; honoraria from Bristol-Myers Squibb, EUSA Pharma, GlaxoSmithKline, Ipsen, Novartis, and Pfizer; and patents, royalties, and other intellectual property from Medical Research Council — Phage Antibody Patents. S. Vázquez Estevez reports honoraria from Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Janssen, Merck Sharp & Dohme, Pfizer, and Roche; and consulting or advisory role with Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Janssen, Merck Sharp & Dohme, Pfizer, and Roche. H. Kalofonos reports consulting or advisory role with Amgen, Genesis, Janssen, Leo, Lilly, Merck, Merck Serono, Merck Sharpe & Dohme, Novartis, Pfizer, and Roche; research funding from Amgen, Bayer, Genesis, Janssen, Lilly, Merck Serono, Merck Sharpe & Dohme, Novartis, Pfizer, and Roche; and travel, accommodation, and expenses from Enorasis, Novartis, Pfizer, and Roche. P. Bono reports stock or other ownership in Tilt Biotherapeutics; and honoraria from Bristol-Myers Squibb, Ipsen, Merck Sharpe & Dohme, Novartis, Orion Pharma, and Pfizer. C. Babanrao Pisal, Y. Hirschberg, L. Dezzani, and Q. Ahmad report employment with Novartis. E. Jonasch reports consulting or advisory role with Bristol-Myers Squibb, Genentech, Novartis, and Pfizer; research funding from Bristol-Myers Squibb, Exelixis, Novartis, and Pfizer; and travel, accommodations, and expenses from Bristol-Myers Squibb, Novartis, and Pfizer. The remaining authors have stated that they have no conflicts of interest.

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